16 JUN 2003

INVESTOR IN PEOPLE

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NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section74(1) and (4) of the Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the international application filed on19 June 2002 under the Patent Cooperation Treaty at the UK Receiving Office. The application was allocated the number PCT/GB2002/02841.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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PCT REQUEST

PG4501B

Original (for SUBMISSION) - printed on 19.06.2002 02:54:24 PM

0	For receiving Office use only	
0-1	International Application No.	PCT/GB 02 / 02841
0-2	International Filing Date	19 JUNE 2002 19/06.2002
0-3	Name of receiving Office and "PCT International Application"	United Kingdom Patent Office PCT International Application
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	PG4501B
I	Title of invention	COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
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II-7	State of residence	GB
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II-9	Facsimile No.	020 8047 6894
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III-1-7	State of residence	GB

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
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IV-1-3	Telephone No.	020 8047 5000
IV-1-4	Facsimile No.	020 8047 6894
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	20 June 2001 (20.06.2001)	
VI-1-2	Number	0115178.6	
VI-1-3	Country	GB	
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	4	-
IX-2	Description	5	-
IX-3	Claims	1	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	3	-
IX-7	TOTAL	14	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	English	

PCT REQUEST

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X-1	Signature of applicant, agent or common representative	
X-1-1	Name (LAST, First)	GIDDINGS, Peter, John

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10-1	Date of actual receipt of the purported international application	19 JUNE 2002 19.06.2002
10-2	Drawings:	
10-2-1	Received	Received.
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

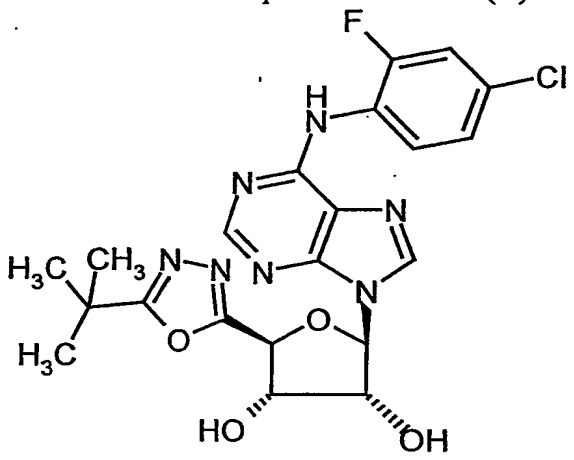
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

Compounds

The present invention relates to heterocyclyl substituted adenosine derivatives. More particularly the invention is concerned with a particular physical form of (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol, pharmaceutical formulations thereof and its use in therapy.

WO99/67262 (Glaxo Group Limited) discloses certain heterocyclyl adenosine derivatives including (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol, Example 14 of WO99/67262, the structure of which is indicated below as the compound of formula (A):



(A)

The preparation of the compound of formula (A) is described in WO99/67262. The compound of formula (A) may be prepared by the reaction of 4-chloro-2-fluoroaniline with an appropriate purinyl derivative having a suitable leaving group in the 6-position of the purine ring, optionally in the presence of a solvent at elevated temperatures. Alternatively the compound of formula (A) may be prepared by treating 9-{(3aR,4R,6S,6aR)-6-[5-tert-butyl-1,3,4-oxadiazol-2-yl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl}-N-(4-chloro-2-fluorophenyl)-9H-purin-6-amine with trifluoroacetic acid followed by treatment with sodium bicarbonate. Extraction of the product into ethyl acetate followed by evaporation *in vacuo* provides the compound of formula (A) as a buff solid.

We have now surprisingly found that the compound of formula (A) can be obtained in polymorphic form.

There is thus provided as a first aspect of the invention (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form.

We have further found that the compound of formula (A) may also be crystallised in the form of polymorphic form II (hereinafter Polymorph II).

There is thus provided in a yet further aspect of the invention (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol as Polymorph II.

Polymorph II exhibits particular stability at elevated temperatures, for example temperatures in excess of 70°C.

Polymorph II may be useful in the preparation of pharmaceutical formulations which may involve temperatures above ambient temperatures.

In a preferred aspect the invention provides (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in the form of Polymorph II as herein defined substantially free of impurities.

In a further preferred aspect the invention (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in the form of Polymorph II as herein defined substantially free of alternative polymorphs.

By "substantially free" is meant containing less than 10%, preferably less than 5%, more preferably less than 2%, of alternative polymorph or impurity.

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol may be prepared in polymorphic form by crystallisation of the compound under suitable conditions.

Polymorph II may be prepared substantially free from other polymorphs by controlling crystallisation conditions.

In general, (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in the form of Polymorph II may be obtained by crystallisation of the compound by heating in methyl isobutyl ketone at reflux (117-118°C) and allowing to cool to ambient temperature, for example 15- 25°C.

Polymorph II may also be prepared by dissolving (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in methyl isobutyl ketone at reflux, filtering, concentrating the filtrate, cooling to 45-70°C, preferably 50-55°C and collecting Polymorph II by filtration.

Alternatively Polymorph II is prepared by dissolving (2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in N,N-dimethylformamide and water wherein the N,N-dimethylformamide:water ratio is from 2:1 to 1:2, optionally treating with decolourising charcoal, adjusting the temperature to greater than 35°C, and optionally seeding with polymorph II. Optionally, toluene may be added prior to collecting the resulting solid.

Interconversion of one polymorph to another can occur under certain circumstances.

The methods for the preparation of polymorphic material, and in particular methods for the preparation of Polymorph II, described herein constitute further aspects of the present invention.

Polymorph II has been characterised by X-ray powder diffraction (XRPD) studies and Raman spectroscopy.

Polymorph II is characterised by having peaks in its Raman spectra at 3424, 1615 and 92 cm^{-1}.

Raman peaks are quoted to the nearest cm-1.

Polymorph II is characterised by having an XRPD pattern with signals at 4.74, 5.34, 6.63, 7.87, 8.31, 8.93, 10.71, and 13.98 (degrees 2-theta).

The skilled person will recognise that XRPD peak positions are affected by differences in sample height. The peak positions quoted herein are thus subject to a variation of +/- 0.15 degrees 2-theta.

This invention further provides for a pharmaceutical composition comprising (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form, and a pharmaceutically acceptable carrier and/or excipient.

Suitable pharmaceutically acceptable carriers and excipients are described in WO 99/967262.

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form may be used for decreasing plasma free fatty acid concentration; reducing heart rate; or treating ischemic heart disease, peripheral vascular disease, stroke, pain, CNS disorder, or sleep apnoea, as described in WO 99/67262.

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form may be used in the manufacture of a medicament for use in decreasing plasma free fatty acid concentration; reducing heart rate; or treating ischemic heart disease, peripheral vascular disease, stroke, pain, CNS disorder, or sleep apnoea, as described in WO 99/67262.

WO 99/67262 (Glaxo Group Limited) is incorporated by reference herein as though fully set forth.

The following examples illustrate the invention but are not intended as a limitation thereof.

EXAMPLES

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol was prepared according to the methods described in WO99/67262.

Example 1 - Preparation of Polymorph II

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol (10g) was taken up in methyl isobutyl ketone (MIBK, 170mL) and the mixture heated to reflux to effect dissolution. The solution was then cooled to ambient over *ca.* 30 mins (crystallisation commenced at *ca.* 70°C) and the thick slurry stirred fo a further hour. The matted crystals were then filtered off, washed with cold MIBK (1x15mL) and dried *in vacuo* at 60°C. Yield: 83%.

Example 2 - Preparation of Polymorph II

(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol (165.8g) was dissolved in MIBK (3800mL) at reflux. The resulting solution was filtered and the filter washed with MIBK (415mL). The combined filtrate and wash were re-heated to reflux and MIBK (1520mL) was removed by distillation under reduced pressure. The residue was cooled to 50°C and the product was collected by filtration, washed with MIBK and then dried *in vacuo* at 40°C to give Polymorph II as an off white solid (130.9g, 75% recovery).

X-Ray Powder Diffraction

The sample preparation and acquisition conditions were as follows:

Samples were lightly ground and packed into silicon cup with a 12 mm (diameter) x 0.5 mm cavity. Data were acquired using a Bruker D8 Advance X-Ray diffractometer configured with a Cu anode, primary and secondary Soller slits, secondary monochromator and scintillation counter. The generator was operated at 40 kV 40 mA. Variable divergence and antiscatter slits were set at 12 mm irradiated area, and the detector slit was set at 0.1 mm. A locked coupled step scan with 0.02 degrees 2 -theta step was used. The sample was rotated.

ata obtained for Polymorph II are shown in Figure 1.

Raman Spectroscopy

Raman spectra were acquired using a Nicolet 960 ESP FT-Raman spectrometer. Samples were held in glass vials; spectra of 5 different points on a sample were averaged. Data collection parameters include: Laser power: 400 mW, Resolution: 4 cm^{-1}, Sample gain: 1.0, Detector: InGaAs, Beamsplitter: CaF2, Correction: none, Zero filling: none, Apodization: Happ-Genzel, Phase correction: Power spectrum.

A Raman spectrum of Polymorphs II is shown in Figure 2.

A photographic image of Polymorph II is shown in Figure 3.

The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of product, process or use claims and may include, by way of example and without limitation, the claims that follow.

CLAIMS

1. (2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form.

2. A polymorphic form according to claim 1 wherein the polymorphic form is Polymorph II.

3. A pharmaceutical formulation comprising a polymorphic form according to claim 1 or claim 2, and a pharmaceutically acceptable carrier and/or excipient.

4. A polymorphic form according to to claim 1 or claim 2 for use in decreasing plasma free fatty acid concentration; reducing heart rate; or treating ischemic heart disease, peripheral vascular disease, stroke, pain, CNS disorder, or sleep apnoea.

5. Use of a polymorphic form according to to claim 1 or claim 2 in the manufacture of a medicament for use in decreasing plasma free fatty acid concentration; reducing heart rate; or treating ischemic heart disease, peripheral vascular disease, stroke, pain, CNS disorder, or sleep apnoea.

6. (2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form substantially as described herein in the specification and/or examples.

Figure 1

X-RAY DIFFRACTION DATA

Polymorph II

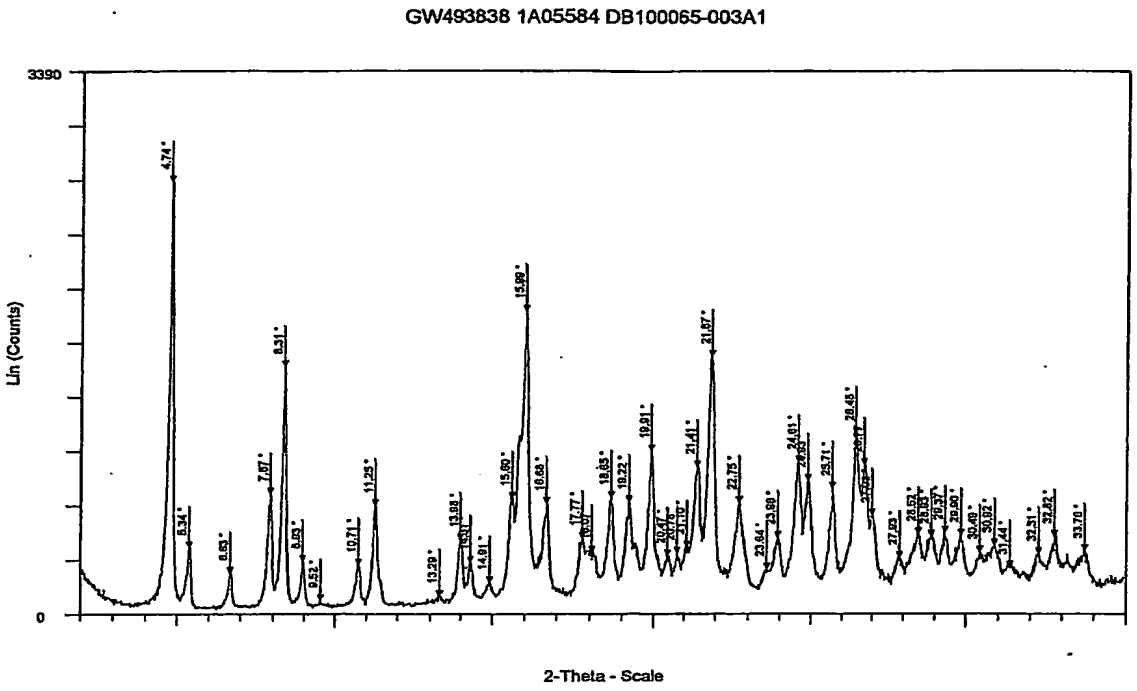


Figure 2

RAMAN SPECTRA

Polymorph II

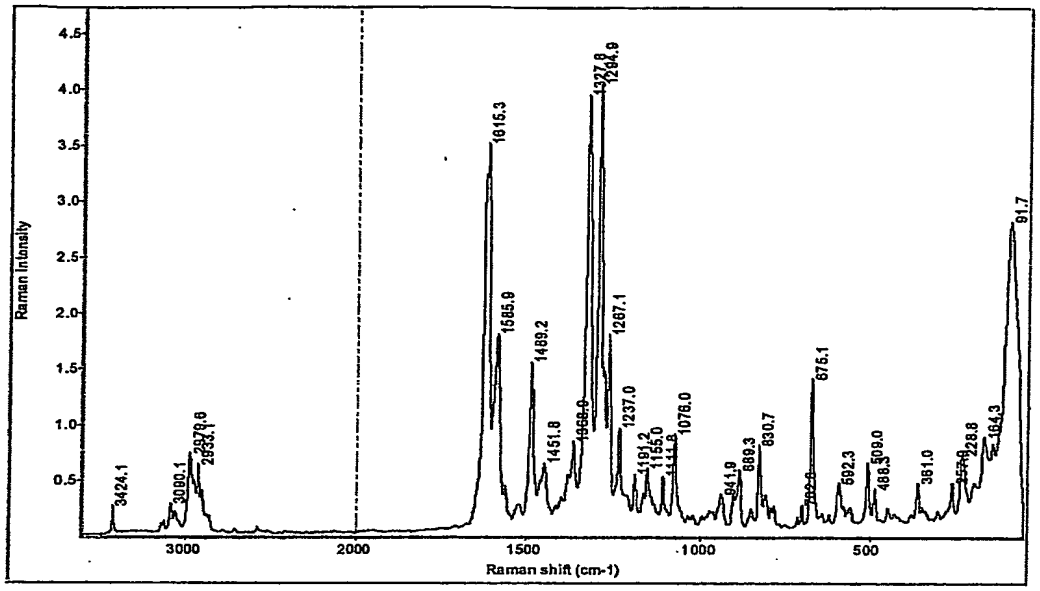
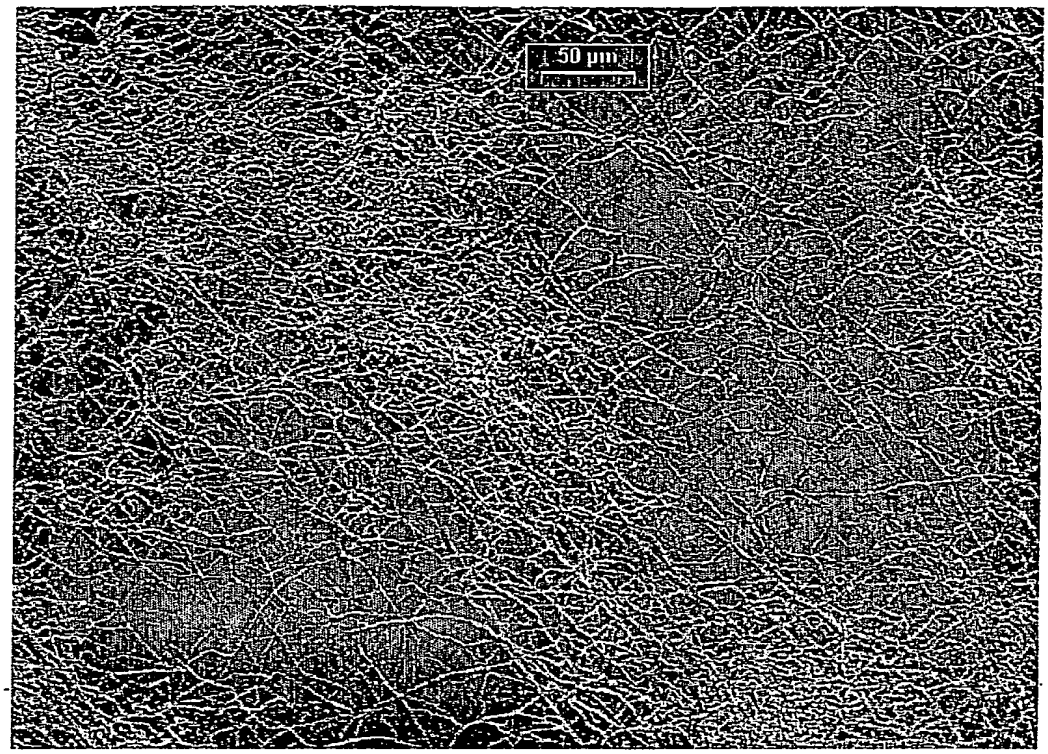


Figure 3

PHOTOGRAPHIC IMAGE OF POLYMORPH II



Form II MIBK

ABSTRACT

(2S,3S,4R,5R)-2-(5-tert-butyl-[1,3,4]-oxadiazol-2-yl)-5-[6-(4-chloro-2-fluorophenylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol in polymorphic form.